Author's response to reviews

Title: Regional disparities in interferon therapy for chronic hepatitis C in Japan: A nationwide, retrospective cohort study

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Author's response to reviews: see over
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Prof. Carl Latkin
Editor
BMC Public Health

Re: Submission of the re-revised manuscript (MS: 1684795701394958) entitled, “Regional disparities in interferon therapy for chronic hepatitis C in Japan: A nationwide retrospective cohort study”

Dear Prof. Latkin,

Please find attached the above re-revised manuscript submitted for publication as an original research article in BMC Public Health. We believe that the findings reported in this study are relevant to the scope of your journal and will be of interest to its readership.

We would like to respond point by point to the Reviewers’ comments;

To Reviewer 1:
1) Some of the concerns were addressed in the revised manuscript but it further in depth reanalysis and interpretation and further hypotheses for the reasons of the disparities are still missing.
   Thanks for your critical review of my revised manuscript. We reanalyzed our results and attempted to find out other interpretation for regional disparities in interferon therapy. We assumed the limited accessibility to medical resources for individual patients would be one of the most influential factors in the regions with low population density, although the actual informations were lacking in this study to our regret. We changed the last sentence of Abstract as follows: “Since the accessibility to medical resources for individual patients seemed to be different among the nine regions, public health actions should be focused on how to construct and properly manage consultation networks between base hospitals and local clinics, especially in those regions with low population density”. And, we added two sentences in Discussion: “Therefore, consultation networks between base hospitals and local clinics should be constructed and properly managed by public health actions, especially in those regions”, at lines 280-283 on page 13, and “Further investigation would be indispensable to evaluate this issue, by analyzing additional factors in those areas, such as a going-to-hospital time, availability of consultation networks between base hospitals and local clinics, and so on”, at lines 339-342 on page 15.

2) Statistical analysis.
   For the multivariate analysis, we did not perform either variable selection or model reduction to avoid inadvertent omission of important variables, according to the advice of Reviewer 2. Since there was a strong correlation between pre-AST and pre-ALT (r = 0.872, P < 0.001), either pre-AST or pre-ALT was included in multivariate analysis as shown in Tables 2 and 3.

To Reviewer 2:
1) The authors replied to a comment by the other reviewer with: 'For the parameters applied to the multivariate analysis, we adopted only the parameters that had a P-value <0.10 by univariate analysis'. However, it is not enough to adapt the statistical modelling methods as described; this choice must also be justified. Why was a P-value threshold chosen, and why <0.10? There are many possibilities for variable selection/model reduction. In the Methods you also should justify why you needed to carry out model reduction, given the large N.

Thanks for your comments. We decided not to perform either variable selection or model reduction to avoid inadvertent omission of important variables. Since there was a strong correlation between pre-AST and pre-ALT (r = 0.872, P < 0.001), either pre-AST or pre-ALT was included in multivariate analysis as shown in Tables 2 and 3.

2) My previous comment 'Which measures and how exactly should they be formulated to match the regional characteristics?' is not addressed by changing 'measures' to 'policies' (perhaps there was some confusion here). What I was asking for was to describe what kind of public health actions would be recommended, and could viably be implemented to address regional disparities. Same applies to my previous Major Comment 5).

Thanks for your patient suggestions. Please forgive me the same response to you as Reviewer 1. We reanalyzed our results and attempted to find other interpretation for regional disparities in interferon therapy. We assumed the limited accessibility to medical resources for individual patients would be one of the most influential factors in the regions with low population density, although the actual informations were lacking in this study to our regret. We changed the last sentence of Abstract as follows: “Since the accessibility to medical resources for individual patients seemed to be different among the nine regions, public health actions should be focused on how to construct and properly manage consultation networks between base hospitals and local clinics, especially in those regions with low population density”. And, we added two sentences in Discussion: “Therefore, consultation networks between base hospitals and local clinics should be constructed and properly managed by public health actions, especially in those regions”, at lines 280-283 on page 13, and “Further investigation would be indispensable to evaluate this issue, by analyzing additional factors in those areas, such as a going-to-hospital time, availability of consultation networks between base hospitals and local clinics, and so on”, at lines 339-342 on page 15.

3) Lines 245-246: 'SVR rates were significantly lower in Hokkaido/Tohoku and Shikoku than in Kyushu' - where/how have you tested this assertion? In the multivariate analysis these regions are only compared with the reference region.

Thanks for your comments. We have changed “than in Kyushu” to “among 9 regions”, as shown at line 223 on page 10 and at line 246 on page 11.

4) Lines 259-261: '...rates of treatment accomplishment and SVR in the
Hokkaido/Tohoku and Shikoku regions were significantly lower than those in the other regions' - same comment as above.

We have changed “than those in the other regions” to “among 9 regions”, as shown at lines 259-260 on page 12.

5) In Tables 2 and 3 (at least), the heading Univariate Analysis should only apply to the P-value column, not the frequencies in the first columns (which are relevant for both analyses). Also, if you are going to report univariate results, reporting the coefficient is essential - not only the P-value - so that the reader can evaluate the impact of the other variables included in the model on a univariate association.

Thanks for your valuable suggestions. We have added “coefficient” to the univariate analysis and changed the heading “Univariate analysis” in Tables 2 and 3, just as you recommended.

6) Line 190: ‘were concentrated on’ - did you rather mean ‘restricted to’?

We have changed the expressions, just as you recommended, at line 190 on page 9.

7) Tables 2 and 3, and text lines 233-234 and 244-245: the Year of treatment grouping is ambiguous: did you mean Before 2009, 2009, and After 2009?

Thanks for your suggestions. We have changed “before 2008” to “before 2008”, and “after 2010” to “2010- (or 2010 and later)”, to avoid misunderstanding, in Tables 2 and 3, at lines 213-214 on page 10, at lines 233-234 on page 11, and at line 244 on page 11.

8) There are still a few grammatical/style errors missed by the English editor, e.g.,’The substantial amount of public money ... urged us to ..’, ‘to build up closer cooperation’, ‘for the numbers of strata’, ’ depopulated areas’ (did you not mean 'areas with low population density’?)

Thanks for your valuable comments.

We have changed as follows: a) “The fact that the substantial amount of public money was allocated for the subsidy policy urged us”, at lines 77-78 on page 5; b) The sentence of “… to build up closer cooperation....” was removed, and replaced by “Therefore, consultation networks between base hospitals and local clinics should be constructed and properly managed by public health actions, especially in those regions”, at line 280-283 on page 13; c) “for the number of strata”, at line 494 on page 21; d) “the regions with low population density”, at line 279 on page 13 and at line 305 on page 14.
We hope that our responses to the reviewers' comments are sufficient to allow publication of our paper in *BMC Public Health*.

We look forward to hearing from you at your earliest convenience.

Yours sincerely,

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